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(2)

OFFICE OF NAVAL RESEARCH

END-OF-THE-YEAR REPORT  
(6/91-5/92)

PUBLICATIONS/PATENTS/PRESENTATIONS/HONORS/STUDENTS REPORT

for

Contract N00014-88-K-0309

R&T Code 413p002

Precomplexation and Activation of Carboxylate and Phosphate Esters

Anthony W. Czarnik

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ELECTED  
MAY 28 1992  
S A D

Ohio State University

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31 May 92

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OFFICE OF NAVAL RESEARCH  
PUBLICATIONS/PATENTS/PRESENTATIONS/HONORS REPORT

R&amp;T Number: 413p002

Contract/Grant Number: N00014-88-K-0309

Contract/Grant Title: Precomplexation and Activation of Carboxylate and  
Phosphate Esters

Principal Investigator: Anthony W. Czarnik

Mailing Address: Dept. of Chemistry, 120 W. 18th Avenue, Columbus, OH 43210

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FAX Number: (614) 292-1685

E-Mail Address: none

## Part I

- (a) Number of papers submitted to refereed journals, but not published: one
- (b) Number of papers published in refereed journals (list attached): one
- (c) Number of books or chapters submitted, but not yet published: none
- (d) Number of books or chapters published (list attached): none
- (e) Number of printed technical reports & non-refereed papers: two
- (f) Number of patents filed: none
- (g) Number of patents granted: none
- (h) Number of invited presentations at workshops or professional society meetings: three
- (i) Number of presentations at workshops or professional society meetings and invited lectures at institutions: six
- (j) Honors/Awards/Prizes for contract/grant employees (list attached): three
- (k) Total number of Graduate Students and Post-Doctoral associates supported by at least 25% during the period, under this R&T project number:
  - Graduate Students: three
  - Post-Doctoral Associates: noneincluding the number of,
  - Female Graduate Students: none
  - Female Post-Doctoral Associates: nonethe number of
  - Minority Graduate Students: none
  - Minority Post-Doctoral Associates: noneand, the number of
  - Asian Graduate Students: one
  - Asian Post-Doctoral Associates: none
- (l) Other funding (list attached)

## Lists to accompany Part I

(b) *Papers Published in Refereed Journals (reprint attached): one*

Fikes, L. E.; Winn, D. T.; Sweger, R. W.; Johnson, M. P.; Czarnik, A. W.  
 "Preassociating  $\alpha$ -Nucleophiles", *J. Am. Chem. Soc.* 1992,  
 114, 1493.

(h) *Invited Presentations at Topical or Scientific/Technical Society Conferences: three*

Invited talk at the Breslow 60th birthday symposium (August 24, 1991)  
 One paper at the ARO CW conference (November 18-22, 1991):

"Preassociating  $\alpha$ -Nucleophiles"

Sixth International Cyclodextrin Symposium (April 21-24, 1991):  
 " $\beta$ -Cyclodextrinyl Hydrazine and Hydroxylamine as Preassociating  
 $\alpha$ -Nucleophiles with Transacylating Activity at pH 7"

(i) *Contributed Presentations at Topical or Scientific/Technical Society Conferences and Invited Lectures at Institutions:*

"Chelation-Enhanced Fluorescence Detection of Metal and Non-Metal Ions  
 in Aqueous Solution"; 19 Jan 92; SPIE Symposium

"Variations on the Polyaniline Motif"; 7 Feb 92; Wright-Patterson  
 Polymer Laboratory

"Chelation-Enhanced Fluorescence. Some Recent Results in Bioorganic  
 Chemistry Brought to Light"; Feb. 26-27, 92; Ball State Univ.

"Artificial Enzymes based on Cyclodextrin"; 25 Mar 92; Clarion  
 University, Clarion, PA

"Artificial Enzymes based on Cyclodextrin"; 13 Apr 92; Indiana State  
 University, Terra Haute, IN

"Chelation-Enhanced Fluorescence Detection of Metal and Non-Metal Ions  
 in Aqueous Solution"; May 8, 92; 3M

(j) *Honors/Awards/Prizes: third year of Camille and Henry Dreyfus  
 Teacher-Scholar Award (1989-1994)*(l) *Other Funding:*

1. A) The National Science Foundation  
 B) "Catalysis via Reversible Covalent Bond Formation"  
 C) amount received this year: \$60,000  
 D) total award: \$171,500  
 E) period covered: 6/15/89-8/31/92

2. A) Petroleum Research Fund of the American Chemical Society  
 B) "Cofacial Derivatives of Hexaazatriphenylene"  
 C) amount received this year: \$20,000  
 D) total award: \$40,000  
 E) period covered: 1/90-9/92

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## Part II

(a) Principal Investigator: Anthony W. Czarnik

(b) Current telephone number: (614) 292-4531

(c) Cognizant ONR Scientific Officer: Dr. Harold E. Guard

(d) Brief (100-200 words) description of project:

The hydrolyses of unactivated esters and amides (both carboxylic and phosphoryl) are exceptionally slow, yet subject to efficient catalysis by enzymes. Because these reactions are key to metabolic processes and to the CW agents designed to interfere with them, the abiotic duplication of transacylase activity remains an eagerly sought-after target. Desirable properties for one class of ideal synthetic transacylase, biotic or abiotic, might include: rapid reaction in totally aqueous solution near neutral pH; activity towards unactivated substrates with turnover behavior; selectivity coupled with a practical ability to bind substrates of widely diverse structural types; an ability to produce the pure catalyst on usefully large scale. To date, no catalyst type meets all of these design criteria. Nevertheless, the past five years has seen such progress that artificial transacylases can no longer be characterized as "pipe dreams."

Our project has focussed sharply on learning what reaction mechanisms lead to the rapid cleavage of unactivated esters and amides at room temperature and neutral pH. Despite their importance, there are very few methods known for accomplishing such conversions. Our group is equally involved in showing how such catalytic groups can be productively coupled with binding groups. We are convinced that such research is a prerequisite to the evolutionary improvement of both biotic and abiotic catalysts.

(e) Significant results during last year (50-100 words):

(1) Synthesis of a binuclear Co(III) complex that does not form an intramolecular  $\mu$ -oxo dimer, but does react with p-nitrophenylphosphate 10-times faster than the parent mononuclear complex.

(2) Conversion of  $\beta$ CDNH<sub>2</sub> to the oxime and evaluation of its reactivity.

(f) Brief (100-200 words) summary of plans for next year's work:

Our current efforts on this topic have been directed towards the use of  $\alpha$ -nucleophiles whose reaction products with carboxylic acid derivatives benefit from metal ion catalysis. However, our interests have been moving toward the more broadly defined questions of: (1) what structural attributes are required in order to observe turnover behavior in reactions accelerated by metal ions; (2) can metals accelerate amide hydrolysis by other than the metal hydroxide or carbonyl polarization mechanisms; (3) can a predicted proximity effect in metal catalyzed hydrolysis be demonstrated experimentally; and, (4) what advantage can be derived from binuclear metal ion catalysis in oriented systems. As we are able, these goals will be pursued.

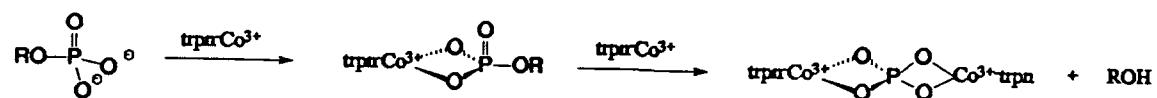
(g) List of names of graduate students and postdoctorals currently working on project: Steven Wathen (G.S.), David Vance (G.S.), David Winn (G.S.).

**Part III**

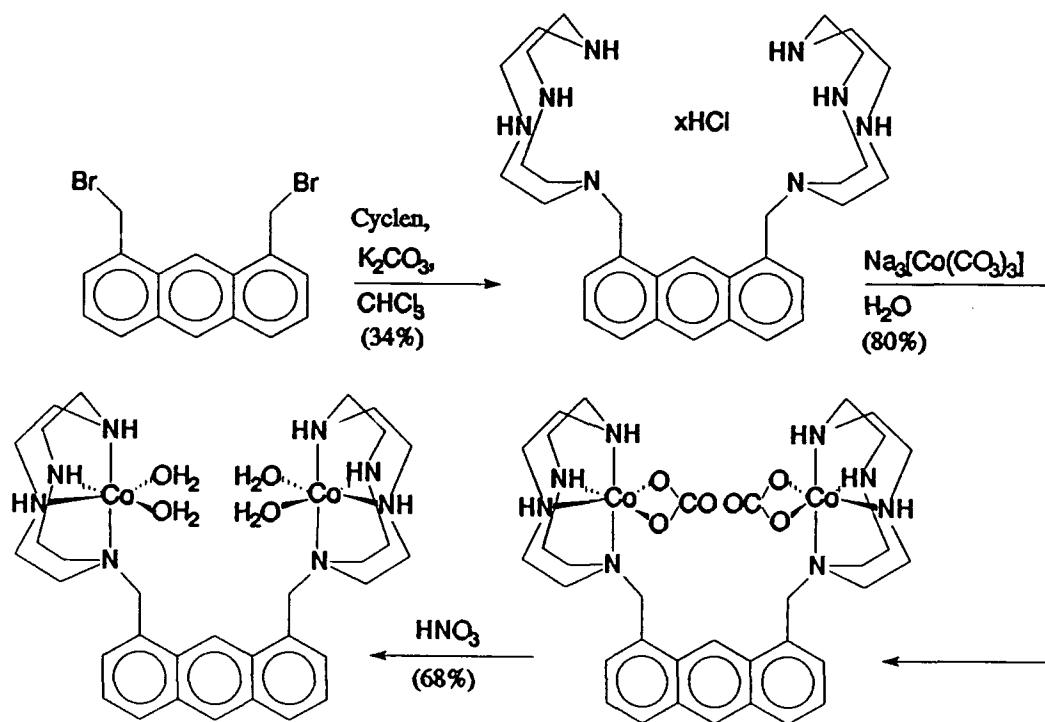
- (a) *An introductory "viewgraph"*: attached as Appendix I
- (b) *A figure*: attached as Appendix II
- (c) *A concluding "viewgraph"*: attached as Appendix III
- (d) *A paragraph of explanatory text*:

The enzyme-like cleavage of phosphate esters under physiological conditions is of great interest due to the biochemical relevance of both naturally-occurring (e.g., DNA) and synthetic (e.g., nerve toxins) derivatives. The cleavage of DNA has been accomplished with specificity through the use of selectively delivered metal ion complexes. However, most of the complexes used to date for this purpose cleave DNA via oxidative mechanisms that do not form religatable ends. We have synthesized and characterized a binuclear Co(III) complex in which the metals are oriented convergently, yet do not form  $\mu$ -oxo dimers. To date, we have shown that the dimer reacts with *p*-nitrophenylphosphate 10-times faster than does two equivalents of the parent cyclen-Co(III) complex. Reactivity towards other phosphate esters is currently being evaluated.

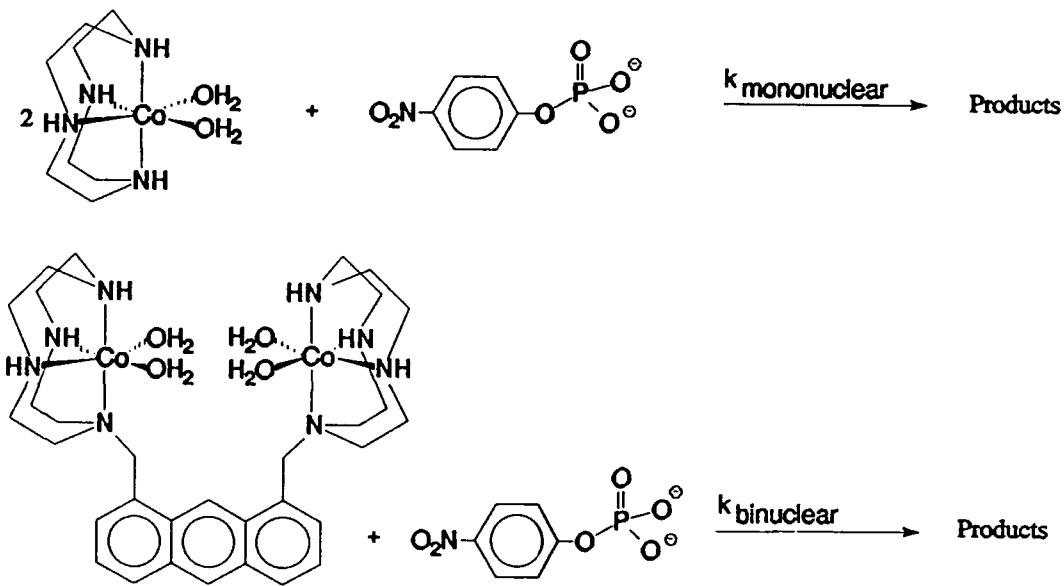
## Appendix I



## Appendix II



## Appendix III



$$\frac{k_{\text{mononuclear}}}{k_{\text{uncatalyzed}}} = 1.6 \times 10^5$$

$$\frac{k_{\text{binuclear}}}{k_{\text{uncatalyzed}}} = 1.6 \times 10^6$$